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Diagnosis and treatment of Sjögren's syndrome

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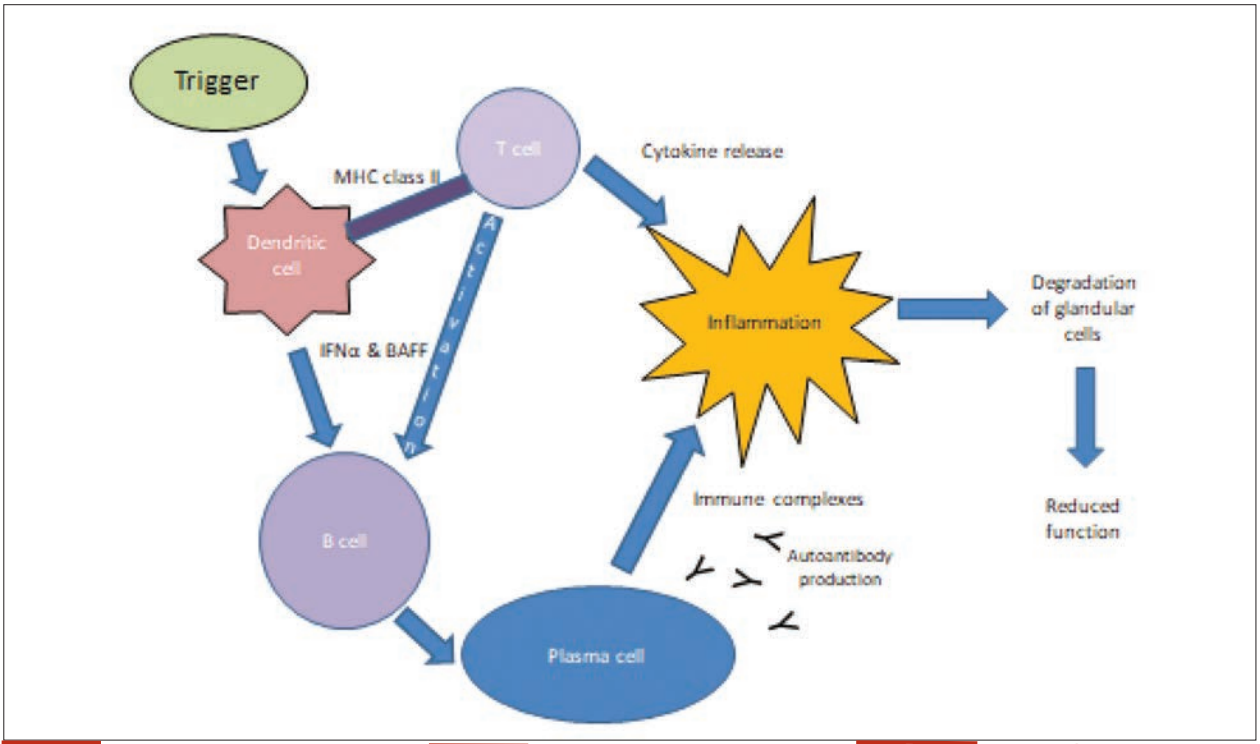

FIGURE 1
Pathophysiology of primary Sjögren's syndrome resulting in exocrine gland destruction

How do patients present in primary care?

PRIMARY SJÖGREN'S SYNDROME IS A CHRONIC SYSTEMIC IMMUNE-MEDIATED condition of unknown aetiology characterised by focal lymphocytic infiltration of exocrine (mainly salivary and lacrimal) glands. It affects 0.1-4.6% of the general population in Europe and 90% of cases are female.[1]

MECHANISMS

The pathophysiology of primary Sjögren's syndrome remains unknown and is likely to be the result of environmental factors triggering inflammation in individuals with a genetic predisposition.

It is accepted that T-cells, B-cells and dendritic cells infiltrate exocrine glands, interfering with their function and causing destruction through cell-mediated and cytokine-activated pathways, leading to chronic inflammation as identified on tissue biopsy, see figure 1, above.

How should diagnosis be confirmed?

PRESENTATION

Sjögren's syndrome often presents in the fifth or sixth decade. However, it can be seen in younger people who tend to present with systemic disease and are less likely to have classical sicca symptoms i.e. dryness of the mouth, eyes or vagina.[2,3]

Although patients generally present with sicca symptoms, other, systemic, symptoms may include arthralgia, fatigue, Raynaud's phenomenon, sensorimotor neuropathy and a dry cough. Peripheral neuropathy can be sensory or sensorimotor, with sensorimotor involvement seen in patients with higher B-cell activity. Cranial neuropathy is rare. The frequency of these symptoms is shown in table 1, left.

Patients may present with arthralgia or a frank inflammatory arthritis as the dominant clinical feature, although on direct questioning many of these patients will report longstanding sicca symptoms.

In patients who develop an inflammatory arthritis, this tends to be »

Table 1

Common symptoms and signs in primary Sjögren's syndrome[4]

Symptoms and signs	Frequency
Raynaud's phenomenon	80%
Fatigue	75%
Dry skin/pruritus	50%
Arthralgia	33-50%
Glandular swelling	25-66%
Dry cough	40%
Sensorimotor neuropathy	< 25%
Purpura rash (hypergammaglobulinaemic)	9%

What are the management approaches?

polyarticular and symmetrical, typically affecting the wrists and small joints of the hands. It is intermittent in nature and usually not deforming or erosive.

Practical tip 1: *Consider primary Sjögren's syndrome as a differential to rheumatoid arthritis in patients presenting with symmetrical inflammatory arthralgia/arthritis affecting the wrists and small joints of the hands.*

Sjögren's syndrome mimics

While Sjögren's syndrome is an important condition to consider in patients presenting with sicca symptoms, a variety of other conditions, drugs and dehydration may contribute to, or cause, mucosal dryness.

Other causes of sicca symptoms include: head and neck radiotherapy (salivary flow can be reduced after the first dose of radiotherapy and this may persist for up to three months post completion), sarcoidosis, acute anxiety, IgG4 disease, hepatitis C, HIV. The latter two are also associated with salivary gland hypertrophy. Chronic ocular conditions (such as blepharitis and conjunctivitis) are a common cause of dry eyes.

The most common drugs which may induce sicca symptoms are highlighted in table 2, below.

Practical tip 2: *Commonly prescribed drugs such as opioids, antidepressants, beta-blockers, proton pump inhibitors, antihistamines and muscarinic antagonists may induce sicca symptoms.*

ASSESSMENT

Because of its complex presentation and heterogeneity, diagnosis may be delayed by 3-11 years.[3]

The presence of any four of the six criteria shown in table 3, p13, is indicative of primary Sjögren's syndrome, as long as either item IV (histopathology) or item VI (serology) is positive. The presence of any three of the four objective criteria (items III, IV, V, VI) is also indicative of the condition.

The following need to be excluded before the classification criteria can be applied:

- Post head and neck radiotherapy
- Hepatitis C infection
- HIV
- Pre-existing lymphoma
- Sarcoidosis
- Graft versus host disease
- Use of anticholinergic drugs (within a time shorter than four times the half-life of the drug)

In patients with a potentially associated disease, for instance, an established diagnosis of rheumatoid arthritis (RA) or another well defined connective tissue disease such as systemic lupus erythematosus (SLE), the presence of item I or item II plus any two from among items III, IV, and V may be considered indicative of secondary Sjögren's syndrome.

Examination findings during a GP consultation may include the following:

- **Eyes:** Dilatation of the conjunctival vessels, corneal lesions, and blepharitis
- **Mouth:** May look dry and a wooden tongue depressor may stick to the tongue. Local infections including oral candidiasis and dental caries are not uncommon
- **Submandibular glands:** May be enlarged but more obvious is bilateral enlargement of the parotid glands. Because of the intermittent nature of glandular swelling, this may be absent at the time of examination
- **Features of other autoimmune disorders** such as RA, SLE, scleroderma and primary biliary cirrhosis

Patients with suspected primary Sjögren's syndrome should be tested for antinuclear antigen (ANA) to look for the presence of anti-Ro/La antibodies which are present in two-thirds of cases. Rheumatoid factor may be present in up to 90% of cases. High levels of IgG are commonly seen in patients with primary Sjögren's syndrome.

Practical tip 3: *Testing for ANA should be performed in all patients with suspected inflammatory arthritis, alongside rheumatoid factor.*

REFERRAL

Referral to a rheumatologist for confirmation of diagnosis (which may involve scintigraphy/sialography, labial gland biopsy) is recommended.

Referral should ultimately be guided by the level of clinical suspicion. Specialist referral should be considered in patients with sicca symptoms who test positive for ANA. However, if a patient is ANA negative but has sicca symptoms, any of the signs and symptoms listed in table 1, p11, and/or suggestive examination findings, then we would also advise referral to a rheumatologist.

Long-term follow-up by a specialist is also required. The general consensus is that patients should be seen every six months by a rheumatologist for those with stable disease, and specific disease activity scores should be incorporated as standard practice.

TREATMENT

Current treatment strategies include a combination of symptom control and immunosuppression, and multidisciplinary involvement. Management of sicca symptoms includes lifestyle changes in combination with topical lubricants.

Patients with dry eyes should be advised not to wear contact lenses, avoid air conditioning where possible and use simple lubricant drops that do not contain preservatives. Liposomal sprays can reduce evaporative tear loss, and lacrimal gland inflammation can be managed by applying damp steamed eye pads. Oral pilocarpine can be

Table 2

Common drugs known to induce sicca symptoms

Class	Drug
Anticholinergic	Antidepressants e.g. amitriptyline Anxiolytics e.g. diazepam Antipsychotics e.g. clozapine
Muscarinic antagonists	Tamsulosin hydrochloride Ipratropium hydrochloride
Antihistamines	Cetirizine hydrochloride, loratadine
Opioids	Morphine, codeine, tramadol
Antihypertensives	Beta-blockers ACE inhibitors
Proton pump inhibitors	Omeprazole

Table 3

Classification criteria for Sjögren's syndrome (sensitivity 97.4%, specificity 89.4%)[5]

Criteria	Evidence	Assessment
I Ocular symptoms	At least one of: **a** Persistent troublesome dry eyes for > 3 months **b** Recurrent sensation of sand or gravel in the eyes **c** Using tear substitutes > 3 times a day	Suitable for assessment in primary care
II Oral symptoms	At least one of: **a** Daily feeling of dry mouth for > 3 months **b** Recurrent or persistent swelling of salivary glands as an adult **c** Frequently drinking liquids to aid in swallowing dry food	Suitable for assessment in primary care
III Ocular signs	Positive Schirmer test or high Rose Bengal score	Performed in secondary care or by community optometrist
IV Histopathology	Focal lymphocytic sialadenitis in minor salivary glands	Salivary gland biopsy in secondary care required
V Objective evidence of salivary gland involvement	Abnormal salivary flow, parotid sialography, salivary scintigraphy	Performed in secondary care
VI Autoantibodies	Antibodies to Ro/SSA or La/SSB antigens, or both	Suitable for assessment in primary care by ordering generic ANA

considered in those with significant symptoms. Ophthalmology input is advisable in severe disease and in patients with inflammatory eye disease, who may require steroid-containing eye drops or ciclosporin.

Dryness of the oral cavity can be managed by reducing sugar and acid intake using pastilles and salivary spray replacement. Dental health is important and patients should see a dentist on a regular basis as they have a higher risk of dental cavities. Toothpaste with a high fluoride content is recommended in addition to intermittent chlorhexidine mouthwash, and regular oral hygiene.

Salivary gland enlargement may occur during acute flares or through duct obstruction from stones or strictures. A short course of oral or intramuscular glucocorticoids often helps and there is anecdotal evidence that local massage may help reduce the swelling.

Management of fatigue as recommended by the NICE guideline includes good sleep hygiene, relaxation techniques, graded exercise programmes and cognitive behaviour therapy.[6]

Systemic features are seen in around 70% of patients[2] and commonly affect joints, lung, skin and peripheral nerves.

Glucocorticoids may be used in systemic flares, or at a low dose to improve sicca symptoms and salivary flow. Hydroxychloroquine may improve joint pain, fatigue, Raynaud's and sicca symptoms, while methotrexate is used in patients with predominant joint involvement (inflammatory arthritis). Stronger disease modifying agents such as azathioprine, methotrexate, cyclophosphamide or mycofenolate mofetil are reserved for serious complications and organ-threatening disease (cytopaenias, lung disease, and neuropathy).

Clinical trials with biologics in Sjögren's syndrome have been disappointing to date, when compared with other rheumatic conditions such as RA.

POTENTIAL COMPLICATIONS

Severe systemic disease occurs in about 15% of patients. This may include interstitial lung disease, myositis, idiopathic thrombocytopaenic purpura, autoimmune liver disease, and renal involvement.[7]

Other autoimmune diseases may be present in association with primary Sjögren's syndrome, including thyroid disease, primary biliary cirrhosis and coeliac disease.

B-cell lymphoma is a serious complication and affects 5-10% of patients with primary Sjögren's syndrome.[8] The risk of developing lymphoma has previously been shown to be 7 to 19 times higher compared with the general population.[9] Predictors for development of lymphoma include: persistent salivary gland enlargement, lymphadenopathy, Raynaud's phenomenon, anti-Ro/La positivity, rheumatoid factor positivity, and low serum C4 levels.[10]

Practical tip 4: *Have a low threshold for assessing and investigating primary Sjögren's syndrome patients presenting with constitutional symptoms.*

Pregnancy poses many challenges and is associated with a higher complication rate in primary Sjögren's syndrome than in the general population.

Obstetric complications include preterm delivery, lower birthweight, and pulmonary hypertension. Anti-Ro antibodies in particular may cross the placenta and induce congenital heart block (occurring in < 2% of pregnancies) and neonatal lupus. The former can be detected by fetal ultrasound, and often »

key points

SELECTED BY

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Primary Sjögren's syndrome is a chronic systemic immune-mediated condition of unknown aetiology characterised by focal lymphocytic infiltration of exocrine (mainly salivary and lacrimal) glands. It affects 0.1-4.6% of the European population and 90% of cases are female. Although it usually presents in the fifth or sixth decade, it can be seen in younger people who tend to present with systemic disease and are less likely to have classical sicca symptoms.

Although patients generally present with sicca symptoms i.e. dryness of the mouth, eyes or vagina, other symptoms may include arthralgia, fatigue, Raynaud's phenomenon, sensorimotor neuropathy or a dry cough. In patients who develop an inflammatory arthritis, this tends to be polyarticular and symmetrical, typically affecting the wrists and small joints of the hands.

While Sjögren's syndrome is an important condition to consider in people presenting with sicca symptoms, a variety of other conditions may contribute to, or cause, mucosal dryness. These include head and neck radiotherapy, sarcoidosis, acute anxiety, IgG4 disease, hepatitis C and HIV. Drugs which may induce sicca symptoms include: opioids, antidepressants, beta-blockers, proton pump inhibitors, antihistamines and muscarinic antagonists. Chronic ocular conditions such as blepharitis and conjunctivitis are a common cause of dry eyes.

On examination the eyes may show dilatation of the conjunctival vessels, corneal lesions, and blepharitis. The mouth may look dry and a wooden tongue depressor may stick to the tongue. Patients are more prone to oral candidiasis and dental caries. There may be bilateral submandibular or, more obviously, parotid gland enlargement. There may be features of other autoimmune disorders such as rheumatoid arthritis, SLE, scleroderma and primary biliary cirrhosis. Patients with suspected primary Sjögren's syndrome should be tested for antinuclear antigen to look for the presence of anti-Ro/La antibodies.

Patients should be referred to a rheumatologist to confirm diagnosis, and this may involve scintigraphy/sialography and/or labial gland biopsy. Treatment comprises symptom control and immunosuppression, and multidisciplinary involvement. Glucocorticoids may be used in systemic flares, or at a low dose to improve sicca symptoms and salivary flow. Hydroxychloroquine may improve joint pain, fatigue, Raynaud's and sicca symptoms, while methotrexate is used in patients with inflammatory arthritis.

Severe systemic disease occurs in about 15% of cases. This may include interstitial lung disease, myositis, idiopathic thrombocytopaenic purpura, autoimmune liver disease, and renal involvement. B-cell lymphoma is a serious complication which affects 5-10% of patients. Pregnancy is associated with an increased risk of complications including preterm delivery, low birthweight, and pulmonary hypertension. Anti-Ro antibodies may cross the placenta and induce congenital heart block and neonatal lupus. anti-Ro positive pregnant women benefit from a joint rheumatology-obstetrics clinic or a multidisciplinary approach.

Neonatal lupus manifests as a transient rash, usually developing during the first few weeks of life and resolving after several weeks to months.

Practical tip 5: *Women of reproductive age who are anti-Ro positive must be counselled about the risk of obstetric complications prior to conception, whenever possible.*

Flares of primary Sjögren's syndrome may also occur during pregnancy. It is advisable that patients have good disease control prior to conception, and that the background medication is continued throughout the pregnancy, if compatible, to minimise the risk of flare. Hydroxychloroquine and azathioprine are both compatible with pregnancy. There is also evidence that low-dose aspirin initiated in early pregnancy can improve placental implantation and reduce pre-eclampsia and intrauterine growth retardation.[2]

Practical tip 6: *It is important that women are encouraged to continue taking their background medication during pregnancy (hydroxychloroquine and/or azathioprine), to minimise the risk of flare.*

Anxiety and depression may occur in a third of patients with Sjögren's syndrome. Management should involve a combination of identifying and managing triggers, social support, psychological intervention (cognitive behavioural therapy) and pharmacological therapy. Amitriptyline, propranolol and selective serotonin reuptake inhibitors can all exacerbate sicca symptoms, thus their use should be considered on a case by case basis.

CONCLUSION

Primary Sjögren's syndrome is a chronic complex systemic disease, which can sometimes lead to significant morbidity and mortality. Prompt recognition and management leads to better outcomes for patients, and vigilance with respect to potential serious complications may reduce morbidity and mortality for these patients.

Competing interests: None

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Useful information

The British Society for Rheumatology guideline for the management of adults with primary Sjögren's syndrome
https://academic.oup.com/rheumatology/article/56/10/e24/3895127

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